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(54) Analgesic preparations

(57) Compositions having enhanced analgesic and myotonolytic activity comprising tizanidine and ibuprofen. The composition is preferably formulated as a tablet and desirably the weight ratio of tizanidine to ibuprofen is from 1:50 to 1:200, especially 1:100.

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SPECIFICATION

Analgesic preparations

The present invention relates to novel pharmaceutical preparations comprising ibuprofen and tizanidine with analgesic and myotonolytic activity as well as to methods of inducing analgesia and of treating conditions associated with increased muscle tone.

Ibuprofen [2-(4-isobutylphenyl)propionic acid] is a known analgesic and anti-inflammatory agent. It is suitable for use in treatment of pain and inflammatory diseases in doses up to 1800 mg daily. However this drug has a potential for adverse side effects, e.g. gastrointestinal side effects such as abdominal pain, indigestion, nausea, gastric ulcus. Furthermore, its effectiveness usually reaches a plateau at the upper limit of its effective dose range above which administration of additional drug does not increase the analagesic or anti-inflammatory effect.

Tizanidine [5-chloro-4-(2-imidazolin-2-ylamino)-2,1,3-benzothiadiazole] is a known myotonolyic agent.

In accordance with the present invention it has now surprisingly been found that administration of a fixed combination of tizanidine and ibuprofen may exhibit particularly advantageous and unforeseen properties, e.g. it may provide excellent analgesic and muscle relaxant activity effectively and rapidly and may be very well tolerated. For example fewer and less serious side effects e.g. gastrointestinal side effects, may be observed. Furthermore, lower amounts of ibuprofen are required for the same analgesic effect.

The analgesic effect and tolerance of the preparation according to the invention may be observed in standard pharmacological tests and in clinical trials.

One pharmacological test is the adjuvans arthritis pain test on the rat [A.W. Pircio et al., Europ. J. of Pharmacology *31*, 207–215 (1975)], effected as follows:

Male rats (OFA strain) weighing 110–120 g were injected subcutaneously with 0.1 ml of a Mycobacterium butyricum suspension in paraffin oil (0.6 mg mycobact. /0.1 ml oil) into the root of the tail. The effects of the test treatment were investigated 18 days later when a marked arthritis in the hindpaws had developed. Thirty minutes before administration the foot joint of the right or the left hindpaw was flexed by means of a Statham transducer until vocalisation occurred. Rats that did not vocalise were discarded from the test. 1, 2, 3 und 5 hours after oral administration of the test substances, the flexion procedure was repeated. The administered pressure was expressed in arbitrary units. The threshold was expressed as the average value of three successive measurements. Those animals in which the threshold was doubled were considered to be protected. Tizanidine is administered p.o. at doses from 0.1 to 15 mg/kg and ibuprofen at doses from 10 to 100 mg/kg p.o. separately or in combination.

Beneficial utility of compositions in accordance with the present invention may also be demonstrated in clinical trials, for example performed as follows:

The trial is carried out on 105 patients, male and female, between the ages of 18 and 70 years. Patients selected exhibit acute low back pain of at least moderate severity, of recent onset, with or without sciatica, together with painful limitation of movement of the lumbar spine.

Patients who were pregnant, breast feeding, with malignancy, osteoporosis, or previous history of lumbar spine surgery or those requiring surgical management were excluded from the study. Also excluded were those with a history of significant systemic disease, allergy or sensitivity to any of the study drugs and those with rheumatic diseases other than osteoarthrosis.

Patients were not allowed to take any other analgesics, anti-inflammatory drugs, antispasmodics, muscle relaxants or anxiolytics, antihypertensives or anticoagulants during the study period.

The trial was effected in a randomised, double-blind design. The patient was allocated to one of two treatment groups, receiving either tablets comprising 4 mg tizanidine and 400 mg ibuprofen 3 times daily (51 patients) or receiving tablets comprising 400 mg ibuprofen 3 times daily (54 patients). Treatment was effected for 7 days.

The doctor assessed the patient on entry to the study (Day 1) and after 3 and 7 days of treatment. The patient was given an information sheet and asked to complete a daily diary.

The doctor was asked to record the following at each assessment:

Date and time of assessments.

Whether the patient has sciatica (absent/mild/moderate/severe).

Pulse rate (beats/min.)

Blood pressure (sitting, systolic and diastolic; mmHg).

Functional capacity (severely restricted, moderately restricted, mildly restricted, not restricted).

Pain on movement (none, mild, moderate, severe).

Pain at rest (none, mild, moderate, severe).

Pain at night (none, mild, moderate, severe).

Whether the patient is able to work (yes, no, not employed).

In addition on Days 3 and 7, the following were assessed:–

Patient's condition compared with first visit (Day 1) (much better, better, same, worse, much worse).

Whether the tablets have helped (no help, some help, very helpful).

Adverse events.

Compliance (tablet count).

Venous blood samples were taken prior to entry into the study, and at the end of th study, to measure the following:

Full blood count, haemoglobin, ESR, aspartate aminotransferase, alanine aminotransferase, gamma-GTP, alkaline phosphatase, bilirubin, total protein, albumin, globulin, uric acid, urea, creatinine, calcium, phosphate glucose, cholesterol and triglycerides.

All patients were asked to complete a daily diary card including visual analogue scales (VAS) comprising:–

Pain on movement. (VAS)

Pain at rest. (VAS)

Pain during the previous night. (VAS)

Pain compared with previous day (better, same, worse).

Interference of pain with daily activities. (VAS)

Treatments were compared using the Mann-Whitney U test, within treatments comparisons were made using the Wilcoxon matched pairs test, from day 1 to day 3 and from day 1 to day 7. These data have been summarised by means and standard deviations (SD) with appropriate P values from the various tests.

Categorical data were summarised by frequency tables and treatments compared using a chi-squared test. Pain intensity categories were combined to give two groups: none/mild and moderate/severe. These tables were analysed using a binomial test. Comparison of assessments within treatments where appropriate, were again done using the Wilcoxon matched pairs test. A binomial test was also used to compare the frequency of specific adverse events in each treatment group.

The following results were obtained:

Significantly fewer patients had moderate or severe pain at night after 3 days' treatment with the combination (18%) than those treated with ibuprofen (37%) [P=0.025]. Fewer patients had moderate or severe pain at rest on Day 3 (P=0.018) and Day 7 (P=0.019) after treatment with the combination compared to those treated with ibuprofen.

Significantly more patients who started the study with moderate or severe sciatica were better after 3 days' treatment with the combination (P=0.039).

The patients' visual analogue scale assessment of pain when walking shows that the combination is significantly better than ibuprofen after 3 days' treatment (P=0.029).

After 3 days treatment, doctors felt that the combination had been helpful to 88% of patients while only 69% derived help from treatment with ibuprofen (P=0.05). After 7 days, these percentages were 89% for the combination and 75% for ibuprofen (P=0.13).

Significantly moe patients treated with ibuprofen suffered gastrointestinal side effects e.g. indigestion, nausea and abdominal pain, than those treated with the combination (P=0.002).

The results of this study show that the combination of tizanidine and ibuprofen has a more rapid onset of action, higher efficacy and less gastro-intestinal side effects than ibuprofen alone.

The combinations of the invention are therefore useful in inducing analgesia, e.g. in the treatment of painful and inflammatory conditions associated with painful muscle spasms, especially for the treatment of painful muscle spasms e.g. due to static and functional disorders of the lumbar or cervical spine (cervical syndrome, acute spasmodic torticollis, low back pain) or postoperative spasms, e.g. following surgery for herniated disk or osteoarthrosis of the hip joint or following accidents causing injury to musculoskeletal system.

In a further aspect the present invention provides a method of inducing analgesia, e.g. treating painful and inflammatory conditions associated with painful muscle spasms e.g. for treating any of specific conditions hereinbefore cited in relation to such treatment, in a subject in need of such treatment, which method comprises administering to said subject a pharmaceutical composition comprising tizanidine and ibuprofen, as well as the use of a pharmaceutical preparation comprising tizanidine and ibuprofen in fixed combination for treatment as defined above.

The exact daily dosage of tizanidine and ibuprofen for use in the method of the invention will of course depend upon, inter alia, the mode of administration and the condition to be treated.

A suitable indicated daily dosage of tizanidine is in the range of from about 1 to about 20 mg, preferably 2 to 12 mg.

An indicated weight ratio of tizanidine to ibuprofen is from about 1:50 to about 1:200, preferably 1:100.

Examples of preferred amounts of tizanidine in unit dosage forms are 1, 2 and 4 mg of tizanidine. Examples of preferred amounts of ibuprofen in unit dosage forms are 100, 200 and 400 mg ibuprofen. Suitably a unit dosage form is administered 1 to 3 times a day. Examples of unit dosage forms are those containing 2 mg tizanidine and 200 mg ibuprofen or 4 mg tizanidine

and 400 mg ibuprofen.

Tizanidine may be administered in free base form or in pharmaceutically acceptable acid addition salt form, e.g. the hydrochloride. Pharmaceutically accpetable salts of ibuprofen are for example potassium, sodium or aluminium salts.

The preparations of the invention include any appropriate form suitable for enteral administration, preferably oral administration and comprising tizanidine and ibuprofen in fixed combination. Preferred preparations in accordance with the invention are forms suiable for oral administration, such as tablets, capsules, dragees, granules or pills. Preferably the preparations of the invention constitute a unit dosage form, whereby each unit dosage will comprise a predetermined amount of tizanidine and ibuprofen.

The preparations of the invention may contain tizanidine and ibuprofen in admixture with suitable pharmaceutical diluents, carriers or other excipients suitably selected with respect to conventional pharmaceutical practice. For example, tablets, capsules, dragees, granules or pills may contain beside the active agents fillers, granulating agents, disintegrating agents, binding agents, lubricating agents, dispersing agents, wetting agents, stabilising agents and dyestuffs.

Additionally, the preparations of the present invention may be formulated in such a manner that the release of the active agents occur only or preferably in a specific part of the inestinal tract, or even the release is sustained to provide controlled release rate of the active agents. Suitable dosage forms for sustained release include tablets coated with a sustained release coating, controlled release polymeric matrices impregnated with the active agents and shaped in tablet form or capsules containing such impregnated polymeric matrices.

The present invention also provides a process for the manufacture of a pharmaceutical preparation, which process comprises bringing tizanidine and ibuprofen into fixed combination, in particular intimately admixing tizanidine and ibuprofen together with a pharmaceutically acceptable diluent or carrier therefor, and optionally forming a unit dosage form.

The following example is illustrative of the preparations of the present invention and their manufacture.

EXAMPLE : Tablet suitable for oral administration

Film coated tablets containing the ingredients indicated below may be prepared by conventional techniques and are useful for oral administration 1 to 3 times a day in the treatment of pain.

Ingredient	*Weight (mg)*
Tizanidine hydrochloride	2.288 (≙ mg base)
Ibuprofen	200.00
Calcium sulfate dihydrate	183.712
Hydroxypropylcellulose	10.00
Maize starch	45.00
Stearic acid	6.00
	450.00
Hydroxypropylmethylcellulose	10.00
	460.00

The ingredients are thoroughly mixed in conventional manner and pressed into individual tablets, each comprising 2 mg free tizanidine and 200 mg free ibuprofen.

CLAIMS

1. A pharmaceutical preparation comprising tizanidine or a pharmaceutically acceptable salt thereof and ibuprofen or a pharmaceutically acceptable salt thereof.
2. A preparation according to claim 1 in unit dosage form.
3. A preparation according to claim 1 in unit dosage form for oral administration.
4. A preparation according to claim 1 in the form of a tablet.
5. A preparation according to claim 1 comprising 1 mg tizanidine.
6. A preparation according to claim 1 comprising 2 mg tizanidine.
7. A preparation according to claim 1 comprising 2 to 4 mg tizanidine.
8. A preparation according to claim 1 wherein the weight ratio of tizanidine to ibuprofen is from 1:50 to 1:200.
9. A preparation according to claim 1 wherein the weight ratio of tizanidine to ibuprofen is 1:100.
10. A process for the manufacture of a pharmaceutical preparation having improved effectiveness in inducing analgesia which process comprises bringing tizanidine and ibuprofen in fixed combination and optionally forming a unit dosage form.

11 A method of inducing analgesis in a subject in need of such inducement, which method comprises administering to said subject an effective amount of a pharmaceutical preparation according to any one of claims 1 to 9.

12 A method for the treatment of painful and inflammatory conditions associated with painful muscle spasms, in a subject in need of such treatment, which method comprises administering to said subject an effective amount of a pharmaceutical preparation according to any one of claims 1 to 9.

13. The use of a pharmaceutical preparation according to any one of claims 1 to 9 for inducing analgesia.

14. The use of a pharmaceutical preparation according to any one of claims 1 to 9 for the treatment of painful and inflammatory conditions associated with painful muscle spasms.

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